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A case of giant invasive prolactinoma in a Royal Australian Air Force aviator prompted a literature review to determine fitness to fly. Particular areas of emphasis included effects and side effects of treatment, particularly bromocryptine therapy, and neurologic and endocrine effects of the tumor. With presently available therapy, this condition was felt to be incompatible with military aviation.

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DEPARTMENT OF THE AIR FORCE
ARMSTRONG LABORATORY (AFMC)
BROOKS AIR FORCE BASE, TEXAS

7 Apr 95

MEMORANDUM FOR WING COMMANDER DAVID L. EMONSON
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FROM: AL/AOCI
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SUBJECT: Review of Case File for Aeromedical Disposition of Prolactinomas

1. I have been asked to review our case file for aeromedical disposition of previous prolactinomas. This is in reference to a subject under review by the Royal Australian Air Force, a case of a commercial and military pilot who presented with a large invasive prolactinoma involving his cavernous sinus and sphenoid sinus, and displacing his optic chiasm and right optic nerve. He was treated with bromocryptine at high doses (20 mg/day), with marked reduction in prolactin levels from "2500 to 140" (presumably ng/ml), and approximately a 50% reduction in tumor size by six months. His neurologic exam and visual fields are reported to be normal on therapy, and he claims to be free of side effects on the medication. He applied for and received medical clearance from the CAA, and is also applying for a waiver for military aviation.

2. Our experience at Brooks with this or similar diagnoses has been limited, since only those aviators with a chance of receiving a waiver are evaluated here. Three cases of pituitary adenomata have been evaluated in the last two decades, and the cases are not parallel, since none was a prolactinoma, all three had been treated with transsphenoidal hypophysectomy, and one had received additional radiation therapy. All had macroadenomata, but none had neurologic deficits. One, a 34-year old pilot seen in 1992, had normal hypothalamic/hypophyseal function, and was waivered for flying duties. Another, a 35-year old helicopter pilot reviewed in 1993, developed panhypopituitarism following surgery, and was permanently disqualified because of lack of adrenal reserve. The third, a 28-year old pilot evaluated in 1978, had surgery followed by irradiation. Endocrine function was normal at the time. He was disqualified, pending re-evaluation in one year to assess pituitary function. The plan was to offer a waiver if his pituitary (especially adrenal) axis remained intact, with presumably annual follow-up thereafter, but he failed to return for follow-up for unknown reasons.

3. None of these cases is particularly pertinent to the RAAF case, but some of the concerns are similar. I am addressing the present aviator's situation on the assumption that he will be continued on bromocryptine therapy, since his adenoma is unlikely to be completely resectable, and radiation therapy would only result in control after several years, if at all. Both these treatment options would carry a significant risk of panhypopituitarism

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even if they were successful in eradicating the tumor. The major issues in this case are the aeromedical risks of drug therapy, potential direct (primarily neurologic) tumor effects, and possible defective pituitary function.

4. Bromocryptine is a semisynthetic ergot alkaloid which directly stimulates neural dopamine receptors. Prolactin is unusual among adenohypophyseal hormones, in that the hypothalamus exerts a predominantly inhibitory rather than stimulatory effect on prolactin-producing cells. Dopamine appears to be the neurotransmitter responsible for that tonic inhibition, and the dopamine agonist action of bromocryptine results both in inhibition of secretion of prolactin, and suppression of lactotroph growth. The drug is very effective; in one prospective multicenter trial, bromocryptine reduced prolactin levels to 11% or less of basal values in 26 of 27 patients with macroprolactinomas, and reduced tumor size by 50% or more in 18 patients and by 10-25% in the remainder. In addition, 9 of 10 patients with visual field cuts showed improvement.[1] As well as a reputation for effectiveness, bromocryptine also has a notable reputation for side effects, which is not surprising given the paternity of the drug. Fully 69% of patients describe significant side effects on starting therapy, though this can be reduced by careful attention to timing and dosage, i.e. starting at a minimal dose and taking care to take the tablet in the middle of a meal. Even then, 5% of patients are unable to continue the drug due to side effects, which include nausea, postural hypotension, and headache.[2] The prevalence of chronic side effects increases with higher dosage, usually defined as greater than 7.5 mg per day. Higher doses are also associated with other symptoms, such as leg cramps, constipation, dry mouth, and peripheral vasospasm in response to cold.[3] Other vasospastic phenomena such as stroke and myocardial infarction have been largely described in postpartum patients, though the potential exists from high doses of any ergot. Other drugs used for hyperprolactinemia include pergolide and lisuride; however, these are also ergot alkaloids, and have a side effect profile at least as significant.[4] A nonergot compound, CV 205-502 (quinagolide), is a dopamine D_2 receptor agonist with fewer side effects. However, the D_2 subtype is the receptor implicated in the pathogenesis of psychosis. While Turner et al noted *de novo* psychosis in 8 of 600 patients treated with bromocryptine or lisuride, neither of which is D_2 specific,[5] Barnett and colleagues described hypomania in 3 of 12 patients on quinagolide, which progressed in one patient to a paranoid psychosis. Furthermore, 11 of 12 developed significant weight loss.[6] We would consider none of these drugs to be compatible with military aviation. Furthermore, we would unfortunately have to consider a self-reported lack of drug-induced side effects in an aviator to be as unreliable as a lack of disease-related symptoms.

5. I am unaware of the direct effects initially shown by this patient's tumor, except that he presented with headaches, although I understand that on treatment his neurologic exam is normal. The risk here is the rapidity of progression that may be shown by these tumors when therapy is withdrawn. The probability of this is difficult to determine, since there are few series of large prolactinomas, and withdrawal of drug therapy in those cases has usually been after surgery or irradiation. The group at the University of Virginia described two patients with large invasive prolactinomas, without prior surgery or radiation therapy, who were followed after cessation of bromocryptine. One, a woman with invasion into the sphenoid sinus, displayed asymptomatic regrowth of tumor within six days.[7] Another, a young man with a large adenoma encroaching on the chiasm and into the sphenoid sinus, had a dramatic response to bromocryptine, with resolution of symptoms and nearly normal visual fields after a year of therapy. Withdrawal of therapy resulted in recurrent headache at 10 days, and recurrent bitemporal hemianopsia by day 13. Bromocryptine was

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reinstituted; his headache resolved after one day, although his visual fields did not normalize for another five months.[8] Two series have attempted to define the risk of regrowth after cessation of therapy. Zárate et al found no evidence of such regrowth of treatment in 12 women with macroadenomata; however, only two had any evidence of suprasellar extension, and both were apparently minor.[9] Johnston and colleagues evaluated withdrawal of bromocryptine in 15 patients with macroadenomata. Six patients had evidence of suprasellar extension at presentation, most of them small; however, one had invasion into the sphenoid sinus; and a seventh was found to have invasion of the sphenoid on a follow-up study. While nearly all had prompt resurgence of prolactin levels off therapy, only one patient was found to have tumor enlargement, noted six weeks after cessation. However, this was one of the two patients with sphenoid sinus invasion, and was the patient with the largest tumor at presentation.[10] While the risk of rapid regrowth off therapy is probably small for the common prolactin-secreting macroadenoma, it appears significant, albeit poorly defined, in patients with large invasive adenomata. Another complication of prolactinomas is CSF rhinorrhea, previously thought to be a result of surgery or radiation therapy, but now well described following tumor shrinkage from medical therapy.[11,12] It is usually listed as rare, but this is to be expected, since it is a complication of large invasive prolactinomas which are themselves rare. In the only series of this type of tumor, 1 in 10 developed CSF rhinorrhea.[13] Not surprisingly, it seems to be those with invasion into the sphenoid sinus who are predisposed to this complication.[9,13] While the risk is probably low in the case of this aviator, such a complication has occurred late, as much as 15 months into therapy.[14] This is consistent with the usual clinical course, since tumors often shrink over a two year period. Another concern is the mortality/morbidity rate. In Davis' series of 10 patients, one died suddenly at age 37 of unexplained cause, another died at age 65 of probable pituitary infarction (having previously presented with a seizure), a third presented at the age of 39 years with *grand mal* seizures, and a fourth, age 22, survived an episode of pneumococcal meningitis.[13] While I can't rule out some referral selection bias, these represented all the patients with giant invasive prolactinomas referred to the endocrine department of one hospital in Birmingham, UK, over a period of years. It is hardly surprising that the morbidity/mortality associated with very large invasive prolactinomas appears to be far higher than the average macroprolactinoma.

6. The last area of concern is pituitary function, especially adrenal reserve. This is critical in a military pilot. Prolonged periods of severe physical/psychological/emotional stress (for that, read warfare) demand significant adrenal reserve. Pharmacologic dosing to match these needs would be the devil's own guessing game. The hazards of inadequate replacement include refractory hypotension and mental status changes. If not already done, it would be relatively easy to evaluate this patient with an ACTH stimulation test, or with the riskier gold standard, an insulin tolerance test. However, there is still a risk that his status would change over time without warning. Such a deficiency might be preceded by symptoms of hypogonadism, but males in general, let alone aviators, are notoriously reluctant to report such symptoms.

7. In summary, if this case were that of a USAF aviator with a large invasive prolactinoma we would unhesitatingly recommend disqualification without waiver from all classes of military aviation. While I can't comment on the CAA, we don't try to reconcile our recommendations with those of our Federal Aviation Administration, since FAA guidelines are derived as much from civil case law as from medical science. However, in all fairness, it should be pointed out that several of the major risks in this case, such as the risk that running out of medication would result in regrowth of tumor, and the risk that stress would

precipitate Addisonian crisis, are peculiar to wartime deployment rather than civil aviation. The only cases of macroadenomas we have entertained for waiver have been cases where surgical or radiologic extirpation has been successful and has not resulted in pituitary insufficiency. Unfortunately, such approaches are probably not reasonable options in the case of this aviator.

8. I hope this has been of help. Please feel free to contact me at DSN 240-3242 or fax, (210)536-4443, if you have any questions.

JEB S. PICKARD, Lt Col, USAF, MC, FS
Chief, Internal Medicine Branch
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cc:
Maj Emmet Murphy

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